REMARKS

This is responsive to the PTO non-final Office Action mailed December 9, 2008 setting a three month period for response. A Request for a Three Month Extension of Time is submitted herewith whereby the period for response is extended to June 9, 2009.

Claims 1, 4-6, 9-13 and 15-16 are amended. Claims 3 and 17 are canceled. Claims 2, 14 and 18 were previously canceled.

The Amendments

Claim 1 has been amended to recite (1) screening a plurality of prodrugs (basis at least in the original claim preamble and specification, page 12, line 33), (2) defining target tissue as a site of viral latency or infection (basis at least is specification page 11, line 26), and (3) a new step (e) of selecting a desired prodrug based on the comparative analysis (basis at least is specification page 8, lines 6 – 20, page 12, line 33 and page 15, lines 22 – 24). The amendments to the remaining claims are editorial.

Withdrawn Rejections

Applicants gratefully acknowledge the withdrawal of the previous rejections under 35 USC 103.

New Rejection under 35 USC 112(2)

All of the claims were rejected under 35 USC 112(2) as being indefinite for the term "target tissue." This rejection should now be moot since the claims now define a target tissue as one which is a site of viral infection or latency. The examiner is respectfully requested to reconsider and withdraw this rejection.

New Rejection under 35 USC 103(a) over Shaw et al. in view of Cook et al.

Claims 1, 3 – 7 and 11 – 13 were rejected under 35 USC 103(a) over Shaw et al. in view of Cook et al.

Shaw et al. disclose determining the bioavailability of a prodrug of PMPA (a methoxyphosphonate nucleotide analogue) in an animal by testing for the presence of drug metabolite in plasma, intestine and liver homogenate. The examiner took the view that Shaw et al. taught assaying a prodrug in a "target" tissue and a "non-target" tissue (liver and intestine, respectfully). Previously, applicants amended claim 1 to remove intestine as a non-target tissue, so the examiner resorted to Cook et al. to provide a teaching of assaying more than one tissue (again, in the context of a bioavailability study).

Cook et al. was another bioavailability study. Cook et al. extended their bioavailability study to an analysis of the tissues in which hydrolysis of their prodrug might have occurred. The purpose of this was to determine which tissue site of hydrolyis was responsible for the bioavailability results in each animal. They administered glycovir to various animals and measured the appearance of the parental drug in intestine, liver, red blood cells and plasma. They concluded that the differences in bioavavailability of glycovir among various animal species were a function of hydrolysis in the small intestine. Thus, Cook et al. do not teach or suggest assaying a plurality of prodrugs in a screening method, nor do they assay tissues known to be sites of infection or latency for the virus against which glycovir is active (HIV). Because they are only concerned with bioavailability they assayed only tissues involved in absorption and metabolism of glycovir, not primary sites of infection by HIV (lymphoid tissues). Red blood cells, liver and intestine are not primary sites of HIV infection. It also should be noted that glycovir is not a methoxyphosphonate analogue.

The fundamental problem with the rejection of the claims over Shaw et al. and Cook et al. is that neither of these references teaches or suggests determining the tissue specificity of their prodrugs *followed by* selecting a prodrug based on those results, i.e., they are not concerned with prodrug

screening. Instead they are concerned with prodrug characterization, more specifically, intraspecies bioavailability (Shaw et al.) and interspecies bioavailability (Cook et al.).

Applicants' claimed invention is intended to exclude bioavailability studies. As noted on page 12, lines 8 – 16 of the specification, the invention is "distinct from studies typically taken to determine oral bioavailability." Determining the bioavailability of prodrugs involves administering a preselected prodrug to a test animal and then determining the distribution of the parental drug (hydrolysis product) as an indicia of prodrug absorption. These studies are lacking step (e) of claim 1, that of selecting from a plurality of prodrugs. Also, since their concern is the ability of the prodrug to be absorbed and the manner in which it is metabolized as part of that absorption, they do not test a target tissue that is a site for viral latency or infection (claim 1, step b). Amended claim 1 now clearly distinguishes bioavailability studies.

The examiner is respectfully requested to reconsider and withdraw this rejection.

New Rejection under 35 USC 103(a) over Shaw et al. in view of Cook et al. and Glazier et al.

Claims 1, 3 – 7, 9 – 13, 15 and 16 were rejected under 35 USC 103(a) over Shaw et al. in view of Cook et al. and Glazier et al.

Glazier et al. (US 5,627,265A1) disclose cell-permeable prodrugs of PMEA in which the phosphorous atom is substituted with a benzyl derivative. Glazier et al. tested the PMEA prodrugs in assays using paired infected and uninfected cell lines (col. 36, lines 35-48; col. 37, lines 5 -22 and Cols. 38-39). In particular, the antiviral activity of a given prodrug was tested in HBV infected hepatocytes and in an uninfected hepatocyte control, and HIV activity was tested in infected and uninfected lymphatic tissue.

Glazier et al. fails to teach or suggest step (b) of claim 1, i.e., assaying a target tissue and a non-target tissue where the target tissue is known to be a site of viral infection and the other is not. Instead, Glazier et al. compare infected and *uninfected* sites of HBV or HIV infection. Stated differently, Glazier et al. do not teach comparing the infected sites with tissues not otherwise susceptible to infection by HBV. Glazier et al. are not concerned with determining if the prodrugs are more active at the sites of infection versus sites not known to be infected. The *only* tissues studied were sites of infection.

Glazier et al. also teach administering a dansyl phosphate prodrug to mice and determining the activity in liver, kidney, blood and spleen. The purpose of this study was to determine the sites of metabolism of their phosphate prodrugs. This is merely a metabolism study and not a comparison of activity in target and non-target tissues, as defined herein. Thus there is no selection step (e) as called for in claim 1.

The examiner urges that it would have been obvious to "combine" the screening methods of Glazier et al. and Shaw et al. because both involve "the determination of the relative antiviral activities of phosphonoamidate prodrugs in various tissue types". The examiner also has taken the position (Office Action mailed Dec. 19, 2006, page 8) that the combination would be desirable because antiviral assays would produce more direct results than the stability assays of Shaw et al. This overlooks the fact that Shaw et al. tested intestine and liver because these are sites of metabolism, not because they are or might be sites of infection. The same can be said for Cook et al., also concerned with bioavailability. Stated differently, Shaw et al. and Cook et al. were conducting bioavailability studies, not antiviral studies, whereas Glazier et al. were conducting an antiviral activity study without any evident concern about bioavailability. Indirectly measuring bioavailability by measuring antiviral activity would introduce an additional variable into the Shaw et al. or Cook et al. studies since the presence of the viral infection would constitute an additional variable potentially masking the metabolism of the prodrug. In addition, a straight insertion of the Glazier et al. method into Shaw et al. or Cook et al. would be anomalous because Glazier et al.

discloses no antiviral assay using intestinal tissue. There would have been no reasonable basis to combine Glazier et al. with Shaw et al. or Cook et al.

As noted, the examiner apparently believes that the result of the combination would be the bioavailability study of Shaw et al. or Cook et al. run with antiviral assays of the sort used by Glazier et al. This would produce antiviral results in different tissues, but since the antiviral assays are for different viruses (each virus for an individual tissue), it would be impossible to compare the *relative* antiviral activities as called for in applicants' claims. In summary, the combination of Glazier et al. and Shaw et al. or Cook et al. fails to meet step d) of claim 1, and it fails to remedy the deficiency of Shaw et al. and Cook et al. in failing to forth a "target tissue." This rejection is now inapplicable in light of the amendments to claim 1.

The examiner is respectfully requested to reconsider and withdraw this rejection.

New Rejection under 35 USC 103(a) over Shaw et al. in view of Cook et al. and Starrett et al.

Claims 1, 3 – 8, 11 – 13 and 17 were rejected under 35 USC 103(a) over Shaw et al. in view of Cook et al. and Starrett et al. The rejection is essentially as set forth above for Shaw et al. and Cook et al., with Starrett et al. being cited for aryl phosphonester prodrugs, hematological target tissue and antitumor activity. This rejection is moot because the claims are no longer directed to antitumor activity. The examiner is respectfully requested to reconsider and withdraw this rejection.

Biesson et al.

The examiner cited Biessen et al. as "pertinent to applicants's disclosure." This reference teaches preparing a prodrug for the treatment of HBV by conjugating PMEA to a ligand recognized by a liver receptor. The authors observe that the two conjugates they made bind preferentially to liver

cells as opposed to kidney (target and non-target tissues). However, Biessen et al. at least fails to disclose step (e) of claim 1 because the Biessen et al. method is not a screening method. Claim 15 also distinguishes this reference since Biessen et al. is limited to hepatotrophic prodrugs.

This application is now believed to be in condition for allowance. An early Notice to that effect is respectfully solicited.

Dated: 6/8/09

Respectfully submitted,

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